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# Epicardial fat in heart failure patients with mid-range and preserved ejection fraction

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## Aims

Adipose tissue and inflammation may play a role in the pathophysiology of patients with heart failure (HF) with mildly reduced or preserved ejection fraction. We therefore investigated epicardial fat in patients with HF with preserved (HFpEF) and mid-range ejection fraction (HFmrEF), and related this to co-morbidities, plasma biomarkers and cardiac structure.

## Methods and results

A total of 64 HF patients with left ventricular ejection fraction >40% and 20 controls underwent routine cardiac magnetic resonance examination. Epicardial fat volume was quantified on short-axis cine stacks covering the entire epicardium and was related to clinical correlates, biomarkers associated with inflammation and myocardial injury, and cardiac function and contractility on cardiac magnetic resonance. HF patients and controls were of comparable age, sex and body mass index. Total epicardial fat volume was significantly higher in HF patients compared to controls (107 mL/m<sup>2</sup> vs. 77 mL/m<sup>2</sup>,  $P < 0.0001$ ). HF patients with atrial fibrillation and/or type 2 diabetes mellitus had more epicardial fat than HF patients without these co-morbidities (116 vs. 100 mL/m<sup>2</sup>,  $P = 0.03$ , and 120 vs. 97 mL/m<sup>2</sup>,  $P = 0.001$ , respectively). Creatine kinase-MB, troponin T and glycated haemoglobin in patients with HF were positively correlated with epicardial fat volume ( $R = 0.37$ ,  $P = 0.006$ ;  $R = 0.35$ ,  $P = 0.01$ ; and  $R = 0.42$ ,  $P = 0.002$ , respectively).

## Conclusion

Heart failure patients had more epicardial fat compared to controls, despite similar body mass index. Epicardial fat volume was associated with the presence of atrial fibrillation and type 2 diabetes mellitus and with biomarkers related to myocardial injury. The clinical implications of these findings are unclear, but warrant further investigation.

## Keywords

Heart failure with preserved ejection fraction • Heart failure with mid-range ejection fraction • Epicardial fat • Atrial fibrillation • Cardiac magnetic resonance imaging

## Introduction

Heart failure (HF) with left ventricular ejection fraction (LVEF) >40% is an increasingly large health problem with a morbidity and mortality similar to HF with reduced ejection fraction (HFrEF, LVEF <40%).<sup>1,2</sup> Despite its increasing prevalence, no specific therapies have been proven beneficial in terms of reducing morbidity and mortality, which could be related to the heterogeneity of the disease.<sup>3</sup> HF with LVEF >40% is characterized by different phenotypes that might require specific treatments.<sup>4,5</sup> Many of these patients are obese and there is increasing evidence that adipose

tissue and the associated inflammation may play a role in the pathophysiology of HF and appears to be a distinct phenotype within the HF spectrum.<sup>6,7</sup>

Epicardial fat has been shown to secrete several pro-inflammatory chemokines and cytokines, collectively called adipokines, in obese patients.<sup>8</sup> Epicardial fat volume was shown to be increased in several systemic diseases, such as the metabolic syndrome and obesity, which are known to induce a systemic pro-inflammatory state.<sup>9–11</sup> Given these associations, it is conceivable that epicardial fat is also involved in the pathophysiology of HF.<sup>8</sup> Due to the close anatomical relation between epicardial

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fat and the myocardium, epicardial fat may have local inflammatory and mechanical effects on the myocardium and the coronary arteries. Via these adipokine-mediated inflammatory mechanisms, 'epicardial' obesity might cause adverse myocardial remodelling in HF, particularly in those with LVEF >40%. The role of epicardial fat has been studied in healthy subjects and in patients with diabetes mellitus using cardiac magnetic resonance (CMR).<sup>12,13</sup> Another study has examined epicardial fat volume in patients with HF<sub>rEF</sub>, and found that it was decreased compared to healthy controls.<sup>11</sup> So far, however, no studies have been conducted in HF patients with LVEF >40%.

In the present study, we therefore investigated the extent and location of epicardial fat volume using CMR. We explored the relation of epicardial fat with co-morbidities, with biomarkers and with myocardial function and contractility parameters on CMR in patients with HF with LVEF >40% and compared these findings to controls. Given the recent distinction between patients with LVEF 40–50% (HF with mid-range ejection fraction, HF<sub>mrEF</sub>) and patients with LVEF >50% (HF with preserved ejection fraction, HF<sub>pEF</sub>), we also examined these two populations separately.

## Methods

### Study population

We enrolled symptomatic HF patients (New York Heart Association functional class ≥II) who had a LVEF >40% on echocardiography. They also had an N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP) level > 125 ng/L and echocardiographic evidence of left ventricular diastolic dysfunction, left atrial dilatation and/or left ventricular hypertrophy, according to the current European Society of Cardiology criteria.<sup>3</sup> All patients underwent standard CMR imaging, and they were excluded for the present analysis if they had LVEF ≤40% on CMR, (corrected) congenital heart disease, or if they had more than moderate left-sided valvular disease. All patients were part of a standard work-up/protocol for HF patients with an LVEF >40%. This protocol consisted of a thorough examination including laboratory testing, echocardiography and CMR if echocardiography was inconclusive about the cause of HF<sub>pEF</sub>. A total of 49 of the 64 HF patients with LVEF >40% participated in the Ventricular Tachyarrhythmia Detection by Implantable Loop Recording in Patients with Heart Failure and Preserved Ejection Fraction (VIP-HF) registry (NCT01989299). This registry was designed to evaluate the incidence of sustained ventricular arrhythmias in patients with HF<sub>pEF</sub>, monitored by implantable loop recorder. The VIP-HF study was approved by the ethics committee of our hospital, and all patients gave written informed consent. The remaining 15 patients were collected from the screening database. Controls were age-, sex- and body mass index (BMI)-matched and underwent CMR mostly because they had a first-degree relative with a cardiomyopathy, so there was an indication for family screening, but the patients were all free of signs and symptoms of HF.

Controls were included if CMR showed no signs of structural heart defects. We excluded those with a documented history of HF, pulmonary hypertension, congenital heart defects, or coronary

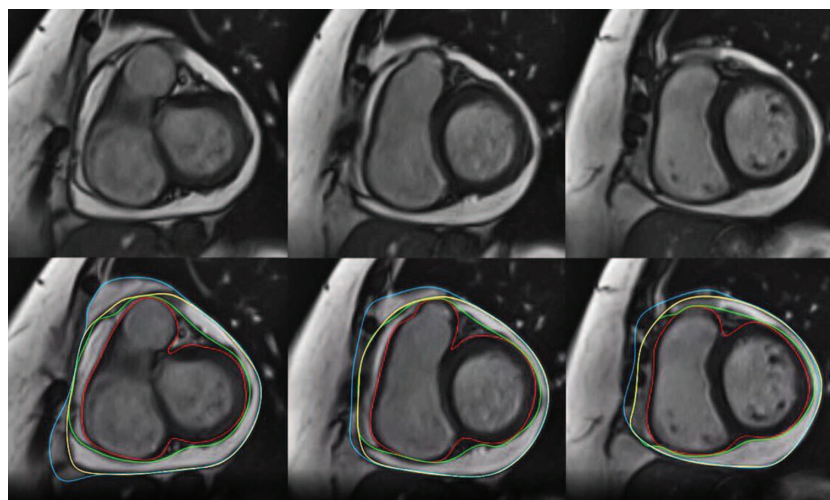
artery disease. The inclusion of controls and non-VIP-HF HF patients was approved by the local ethics committee. This study was in concordance with the principles outlined in the Declaration of Helsinki.

### Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging was performed using a standard protocol for the acquisition of cardiac volumes and functional parameters, as previously published by our group.<sup>14</sup> In short, all CMR studies were performed using a 1.5 Tesla scanner (Siemens, Erlangen, Germany). ECG-triggered cine loop images were obtained during breath hold at end-expiration, using a retrospectively gated cine steady-state free-precession sequence. Approximately 15 short-axis slices from base to apex were obtained, including both atria.

Cardiac magnetic resonance images were analysed off-line by two observers (G.v.W. and T.M.G.) using dedicated software (QMass 7.6, QStrain 2.0, Medis, Leiden, The Netherlands). Endocardial and epicardial borders of the left and right ventricle were manually delineated on the end-diastolic and end-systolic phases on the short-axis stacks. End-diastolic and end-systolic volumes were automatically calculated by the summation of slices multiplied by slice thickness method. Volumetric measurements were indexed for body surface area (BSA). Using the long-axis slices, left atrial and right atrial volumes were measured by tracing the area and length of both atria in end-systole and end-diastole. Atrial volume was approximated using the area–length method.<sup>15</sup> To assess ventricular contractility, tissue tracking analysis was performed on cine imaging. Strain was measured as the total deformation of the myocardium from its baseline length to its maximum length, and is expressed as a percentage.<sup>16</sup> Left ventricular circumferential strain was measured on the short axis at base, mid-ventricular and apical level, left ventricular longitudinal strain was measured on the four-chamber and two-chamber cine images, and right ventricular longitudinal strain was measured on the four-chamber view.

Epicardial fat is the adipose tissue situated between the outer wall of the myocardium and the visceral layer of the pericardium.<sup>17,18</sup> Epicardial fat was manually delineated on end-diastolic short-axis slices, working from the most basal slice towards the most apical slice (Figure 1).<sup>18,19</sup> The mitral valve annulus position was used to differentiate between atrial and ventricular epicardial fat. Epicardial fat volumes were calculated by summation of epicardial fat volume of each slice using the modified Simpson's rule.<sup>20</sup> All epicardial fat measurements were done by one investigator (G.v.W.) after training. All epicardial fat measurements were reviewed by a second fully blinded observer (T.P.W.) who randomly checked the measurements by repeating them. No variability of >10% was found between the observers. In addition, the presence of epicardial fat was verified by measuring pre- and post-contrast T1 times of the myocardium, epicardial fat, subcutaneous fat, and the blood pool using T1 mapping at mid-ventricular level. This way, it was ensured that epicardial fat volume included primarily adipose tissue and not fluids, since T1 times of epicardial fat and subcutaneous fat were comparable.



**Figure 1** Upper figure shows a short-axis series, moving from basal to apical slices. The myocardium is shown in red, the visceral layer of the pericardium in green, the parietal layer of the pericardium in yellow, the pericardial fat border in blue.

## Echocardiography

Echocardiographic parameters were assessed according to the current recommendations for cardiac chamber quantification and included: left ventricular and right ventricular systolic function, left ventricular diastolic function (E, A, E/A ratio, e', and E/e' ratio), valvular stenosis and/or regurgitation, and the peak pressure gradient across the tricuspid valve.<sup>21</sup> In addition, the absence of pericardial effusion to ensure the reliability of epicardial fat measurements was also verified on echocardiography.

## Biomarkers

Plasma biomarkers for HF (NT-proBNP), inflammation [C-reactive protein (CRP) and leucocytes], myocardial damage [troponin T, creatine kinase muscle–brain fraction (CK-MB)], type 2 diabetes mellitus [glycated haemoglobin (HbA<sub>1c</sub>)] and renal function [estimated glomerular filtration rate (eGFR)] were obtained from medical records within 3 months before or after CMR imaging. Plasma biomarkers were not available for controls.

## Statistical analysis

Data are presented as numbers (percentage), mean  $\pm$  standard deviation or median with interquartile ranges, depending on distribution. Differences in continuous variables between groups were analysed using the independent samples *t*-test or Wilcoxon rank test, depending on distribution. Differences in categorical variables between groups were analysed using the Chi-squared test or Fisher's exact test. Correlations between clinical, CMR and biomarker parameters with the amount and location of epicardial fat were analysed using Pearson's or Spearman's correlation, depending on distribution. Associations between epicardial fat, clinical parameters and HF were analysed using a multivariable linear regression model. All biomarkers, except eGFR, were log

transformed prior to the analysis. Statistical analyses were performed using SPSS (version 23, SPSS Inc., Chicago, IL, USA). Statistical significance was considered at a *P*-value  $<0.05$ .

## Results

### Patient characteristics

We examined 70 HF patients with LVEF  $>40\%$  and 20 controls. In six HF patients (8.5%), the atria were not included in the short-axis measurements, and therefore total epicardial fat could not be calculated and these patients were excluded. The final study population thus consisted of 64 HF patients and 20 controls. Patient characteristics of the study population are depicted in Table 1. There were no significant differences regarding age, sex, and BMI between HF patients and controls. Characteristics of HFpEF and HFmrEF patients are depicted in the online supplementary Table S1. NT-proBNP was higher in HFmrEF compared to HFpEF.

### Epicardial fat and cardiac function in heart failure versus controls

Despite similar BMI, total and ventricular epicardial fat volume was significantly increased in HF patients compared to controls (total fat: 107 mL/m<sup>2</sup> vs. 77 mL/m<sup>2</sup> and ventricular fat: 80 mL/m<sup>2</sup> vs. 53 mL/m<sup>2</sup>; all  $P < 0.001$ ) (Table 2). In a multivariable regression model including age, sex, BMI, diabetes mellitus and atrial fibrillation, HF remained an independent correlate with total epicardial fat ( $P = 0.003$ ). Interestingly, epicardial fat volume around the atria was not different between HF patients and controls ( $P = 0.2$ ).

Left ventricular end-systolic volume was higher in HF patients compared to controls (43 mL/m<sup>2</sup> vs. 35 mL/m<sup>2</sup>,  $P = 0.02$ ), whereas LVEF was lower in HF patients compared to controls (54% vs. 60%,  $P = 0.002$ ). No differences were found in right ventricular

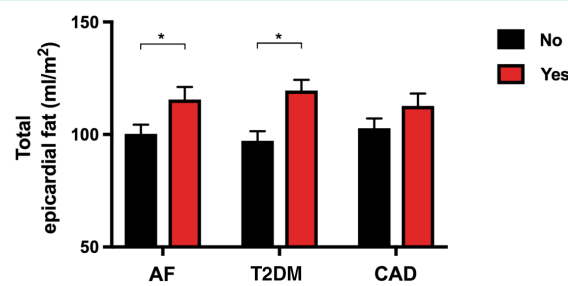
**Table 1** Patient characteristics

|                                    | HF patients<br>(n = 64) | Controls<br>(n = 20) | P-value |
|------------------------------------|-------------------------|----------------------|---------|
| Age (years)                        | 70 ± 10.7               | 66 ± 5.5             | 0.1     |
| Male sex, n (%)                    | 40 (63)                 | 13 (65)              | 0.9     |
| Body weight (kg)                   | 87.0 ± 20.3             | 84.1 ± 13.3          | 0.5     |
| BSA (m <sup>2</sup> )              | 2.0 ± 0.3               | 2.0 ± 0.2            | 0.9     |
| BMI (kg/m <sup>2</sup> )           | 29.6 ± 5.7              | 27.2 ± 4.6           | 0.08    |
| Systolic BP (mmHg)                 | 139 ± 22.4              | NA                   |         |
| Diastolic BP (mmHg)                | 72 ± 12.3               | NA                   |         |
| Heart rate (b.p.m.)                | 73.3 ± 11.9             | NA                   |         |
| Co-morbidities, n (%)              |                         |                      |         |
| Atrial fibrillation                | 28 (44)                 | 2 (10)               | 0.006   |
| Hypertension                       | 48 (75)                 | 7 (35)               | 0.001   |
| CAD                                | 27 (42)                 | 0 (0)                | <0.0001 |
| T2DM                               | 28 (44)                 | 3 (15)               | 0.02    |
| NYHA class                         |                         |                      |         |
| II                                 | 32 (50)                 | 0                    |         |
| III                                | 32 (50)                 | 0                    |         |
| Medication, n (%)                  |                         |                      |         |
| ACEI                               | 25 (39)                 | 4 (20)               | 0.1     |
| ARB                                | 22 (34)                 | 4 (20)               | 0.2     |
| Beta-blockers                      | 58 (91)                 | 6 (30)               | <0.0001 |
| MRA                                | 24 (38)                 | 0 (0)                | 0.001   |
| Diuretics                          | 57 (89)                 | 4 (20)               | <0.0001 |
| Statins                            | 34 (53)                 | 11 (55)              | 0.9     |
| Echo parameters                    |                         |                      |         |
| Mean septal lateral e'             | 7.8 ± 2.1               | 9.6 ± 3.2            | 0.02    |
| E/e'                               | 10.1 (8.5–16.6)         | 8.2 (6.2–12.2)       | 0.07    |
| E/A ratio                          | 1.1 (0.7–1.5)           | 0.8 (0.7–1.0)        | 0.5     |
| Biomarkers                         |                         |                      |         |
| NT-proBNP (ng/L)                   | 885 (451–1517)          | NA                   |         |
| Troponin T (ng/L)                  | 19 (10–39)              | NA                   |         |
| CK-MB (U/L)                        | 14 (12–19)              | NA                   |         |
| CRP (mg/L)                         | 4.4 (1.9–9.7)           | NA                   |         |
| Leucocytes (10 <sup>9</sup> /L)    | 7.7 (6.0–9.7)           | NA                   |         |
| HbA <sub>1c</sub> (mmol/mol)       | 44 (40–57)              | NA                   |         |
| eGFR (mL/min/1.73 m <sup>2</sup> ) | 58.9 ± 26.1             | NA                   |         |

Quantitative data are presented as mean ± standard deviation, or median with interquartile ranges. Qualitative data are presented as number (%).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; BSA, body surface area; CAD, coronary artery disease; CK-MB, creatine kinase muscle–brain fraction; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, glycated haemoglobin; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NA, not available; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; T2DM, type 2 diabetes mellitus.

volume and function between groups. Right ventricular contractility measured by longitudinal strain, however, was lower in HF patients compared to controls (20% vs. 23%,  $P = 0.02$ ). Both left and right atrial volumes were markedly larger in HF patients than in controls (all differences between HF and controls  $P < 0.005$ ). CMR characteristics for HFpEF and HFmrEF are displayed in the online supplementary Table S2. LVEF and right ventricular ejection



**Figure 2** Bar charts comparing total epicardial fat volume (mL/m<sup>2</sup>) in different co-morbidities in heart failure. \* $P < 0.05$ . Atrial fibrillation (AF,  $P = 0.03$ ), type 2 diabetes mellitus (T2DM,  $P = 0.001$ ), coronary artery disease (CAD,  $P = 0.16$ ). Error bars represent standard error of the mean.

fraction were higher in the HFpEF group. Epicardial fat volumes were comparable between groups.

### Associations between epicardial fat and co-morbidities and plasma biomarkers

Body mass index and body surface area were not associated with the extent of epicardial fat volume in HF patients (Table 3). In contrast, HF patients with type 2 diabetes mellitus and/or atrial fibrillation had higher epicardial fat volumes than HF patients without these co-morbidities (120 mL/m<sup>2</sup> vs. 97 mL/m<sup>2</sup>,  $P = 0.001$ ; and 116 mL/m<sup>2</sup> vs. 100 mL/m<sup>2</sup>,  $P = 0.03$ , respectively) (Figure 2). There were no significant correlations between patient characteristics and atrial epicardial fat. For controls, there were no associations between any of the patient characteristics and total epicardial fat volume.

Elevated plasma levels of troponin T, CK-MB and HbA<sub>1c</sub> were associated with increased total epicardial fat volume (Figure 3). eGFR showed a negative correlation with total epicardial fat volume. There were no significant associations between epicardial fat and NT-proBNP, CRP, or leucocytes in patients with HF.

### Associations between epicardial fat and cardiac function and dimensions on cardiac magnetic resonance imaging

Left ventricular end-systolic volume was positively associated with total epicardial fat, whereas LVEF was inversely associated with total epicardial fat (both  $R = -0.27$ ,  $P = 0.03$ ) (Table 3). In addition, global longitudinal and circumferential strain were negatively correlated with total epicardial fat ( $R = -0.34$ ,  $P = 0.006$ ; and  $R = -0.32$ ,  $P = 0.009$ , respectively). No associations were found between right ventricular parameters and total epicardial fat volume, except for right ventricular end-diastolic mass index ( $R = 0.34$ ,  $P = 0.005$ ). Higher left and right atrial volumes were associated with higher total epicardial fat volume (left and right atrial end-systolic volume index, both  $R = 0.28$ ,  $P = 0.03$ ). Only left atrial end-systolic volume



**Table 2** Cardiac magnetic resonance imaging characteristics

|   | HF patients (n = 64) | Controls (n = 20) | P-value |
|---|----------------------|-------------------|---------|
| Adipose tissues                                 |                      |                   |         |
| Total epicardial fat (mL/m <sup>2</sup> )       | 107.0 ± 27.7         | 76.9 ± 11.5       | <0.0001 |
| Ventricular epicardial fat (mL/m <sup>2</sup> ) | 80.1 ± 19.9          | 52.7 ± 11.1       | <0.0001 |
| Atrial epicardial fat (mL/m <sup>2</sup> )      | 26.8 ± 12.7          | 24.2 ± 6.4        | 0.2     |
| Volumes and function                            |                      |                   |         |
| LVEF (%)  | 54.3 ± 8.5           | 59.7 ± 5.4        | 0.002   |
| LVEDVI (mL/m <sup>2</sup> )                     | 91.5 ± 22.3          | 85.8 ± 21.5       | 0.3     |
| LVESVI (mL/m <sup>2</sup> )                     | 42.7 ± 15.6          | 35.0 ± 11.6       | 0.02    |
| LVEDMI (g/m <sup>2</sup> )                      | 51.7 ± 17.9          | 57.6 ± 10.0       | 0.07    |
| LVCI (L/min/m <sup>2</sup> )                    | 3.3 ± 0.6            | 3.6 ± 0.8         | 0.2     |
| RVEF (%)  | 55.6 ± 11.3          | 53.3 ± 6.5        | 0.3     |
| RVEDVI (mL/m <sup>2</sup> )                     | 84.0 ± 20.4          | 89.7 ± 13.6       | 0.2     |
| RVESVI (mL/m <sup>2</sup> )                     | 38.1 ± 15.2          | 41.8 ± 8.2        | 0.2     |
| RVEDMI (g/m <sup>2</sup> )                      | 19.0 ± 5.2           | 18.3 ± 2.1        | 0.4     |
| RVCI (L/min/m <sup>2</sup> )                    | 3.1 ± 0.7            | 3.4 ± 0.8         | 0.2     |
| LAESVI (mL/m <sup>2</sup> )                     | 66.4 ± 24.1          | 36.7 ± 14.5       | <0.0001 |
| LAEDVI (mL/m <sup>2</sup> )                     | 45.0 ± 24.3          | 18.6 ± 12.4       | <0.0001 |
| RAESVI (mL/m <sup>2</sup> )                     | 51.2 ± 24.5          | 36.8 ± 14.2       | 0.002   |
| RAEDVI (mL/m <sup>2</sup> )                     | 37.7 ± 23.9          | 17.7 ± 8.1        | <0.0001 |
| Strain  |                      |                   |         |
| LV global longitudinal strain (%)               | 19.8 ± 5.1           | 21.3 ± 4.4        | 0.3     |
| LV global circumferential strain (%)            | 29.4 ± 10.0          | 30.1 ± 6.7        | 0.7     |
| RV global longitudinal strain (%)               | 19.9 ± 6.1           | 23.4 ± 5.8        | 0.02    |

Data are presented as mean ± standard deviation.

HF, heart failure; LAEDVI, left atrial end-diastolic volume index; LAESVI, left atrial end-systolic volume index; LV, left ventricular; LVCI, left ventricular cardiac index; LVEDMI, left ventricular end-diastolic mass index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; RAEDVI, right atrial end-diastolic volume index; RAESVI, right atrial end-systolic volume index; RV, right ventricular; RVCI, right ventricular cardiac index; RVEDMI, right ventricular end-diastolic mass index; RVEDVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume index.

index was associated with atrial epicardial fat volume ( $R = 0.26$ ,  $P = 0.04$ ). In control patients, no CMR parameters were associated with total epicardial fat volume.

## Discussion

In the present study, we found that HF patients with LVEF >40% had more epicardial fat compared to controls, despite similar BMI. Also, increased epicardial fat volume was more common in patients with type 2 diabetes mellitus and to a lesser extent also in patients with atrial fibrillation. Lastly, epicardial fat was associated with biomarkers of myocardial damage, glucose metabolism, and renal dysfunction. To our knowledge, this is the first study that comprehensively quantified the amount and location (total vs. ventricular vs. atrial) of epicardial fat in HF with LVEF >40%.

In contrast to previous studies, epicardial fat was not associated with BMI.<sup>6</sup> BMI is an estimate of the overall fat status, but does not capture information about body fat distribution. It is plausible that this is the explanation why we did not find differences in BMI, but only in epicardial fat.

Increased adipose tissue, especially around internal organs, is indisputably associated with metabolic and haemodynamic alterations in the body.<sup>12,13,22</sup> In adiposity, fat cells tend to

hypertrophy and become dysfunctional due to the surplus of energy.<sup>23</sup>

When fat cells become dysfunctional, they may start to release pro-inflammatory adipokines into the bloodstream, possibly leading to a chronic systemic inflammatory state associated with arterial stiffness, endothelial dysfunction of arterioles, and fibrosis, which are all implicated in the development of HF with LVEF >40%.<sup>6,22,24,25</sup> One can postulate this same mechanism may hold true for epicardial fat. This way, it is suggested epicardial fat may affect the myocardium by directly releasing adipokines near the cardiomyocytes or via the vasa vasorum where adipokines may interact with the myocardium downstream causing cardiac endothelial dysfunction and remodelling, possibly leading to HF with LVEF >40% and/or atrial fibrillation.<sup>26,27</sup> For HFrEF, epicardial fat may yield different effects on the myocardium, as in these patients the pathophysiological mechanism resulting in HF differs from those with HF with LVEF >40% and epicardial fat seems to be reduced compared to controls instead of increased.<sup>11,28</sup> On the other hand, epicardial fat may also negatively impact cardiac performance by a direct mechanical effect caused by increased pericardial restraint and enhanced ventricular interdependence, as recently shown in a haemodynamic exercise study in patients with HFpEF.<sup>6</sup> Unfortunately for the present study, dynamic exercise CMR was

**Table 3** Associations between epicardial fat, patient characteristics and cardiac magnetic resonance parameters

|                                  | HF patients (n = 64) |          |                            |           |                       |          | Controls (n = 20)    |          |
|----------------------------------|----------------------|----------|----------------------------|-----------|-----------------------|----------|----------------------|----------|
|                                  | Total epicardial fat |          | Ventricular epicardial fat |           | Atrial epicardial fat |          | Total epicardial fat |          |
|                                  | R                    | P-value* | R                          | P-value** | R                     | P-value† | R                    | P-value‡ |
| Age                              | 0.023                | 0.9      | 0.01                       | 0.9       | 0.03                  | 0.8      | 0.13                 | 0.6      |
| Body weight                      | 0.04                 | 0.7      | 0.001                      | 0.99      | 0.09                  | 0.5      | 0.02                 | 0.9      |
| BSA                              | 0.02                 | 0.9      | -0.009                     | 0.9       | 0.06                  | 0.6      | -0.06                | 0.8      |
| BMI                              | 0.15                 | 0.3      | 0.09                       | 0.5       | 0.17                  | 0.2      | 0.14                 | 0.6      |
| Systolic BP                      | -0.15                | 0.3      | -0.05                      | 0.7       | -0.25                 | 0.05     | NA                   | NA       |
| Diastolic BP                     | 0.14                 | 0.3      | 0.07                       | 0.6       | 0.18                  | 0.2      | NA                   | NA       |
| Heart rate                       | 0.09                 | 0.5      | 0.04                       | 0.8       | 0.13                  | 0.3      | NA                   | NA       |
| Echo parameters                  |                      |          |                            |           |                       |          |                      |          |
| Mean septal lateral e'           | -0.04                | 0.8      | -0.01                      | 0.9       | -0.07                 | 0.6      | -0.32                | 0.3      |
| E/e'                             | 0.27                 | 0.07     | 0.171                      | 0.3       | 0.17                  | 0.3      | -0.45                | 0.2      |
| E/A ratio                        | 0.40                 | 0.007    | 0.33                       | 0.03      | 0.11                  | 0.5      | 0.59                 | 0.2      |
| Biomarkers                       |                      |          |                            |           |                       |          |                      |          |
| NT-proBNP                        | 0.20                 | 0.1      | 0.15                       | 0.3       | 0.2                   | 0.1      | NA                   | NA       |
| Troponin T                       | 0.35                 | 0.01     | 0.32                       | 0.02      | 0.29                  | 0.04     | NA                   | NA       |
| CK-MB                            | 0.37                 | 0.006    | 0.28                       | 0.04      | 0.38                  | 0.005    | NA                   | NA       |
| CRP                              | 0.09                 | 0.5      | 0.04                       | 0.7       | 0.13                  | 0.3      | NA                   | NA       |
| Leucocytes                       | 0.03                 | 0.8      | 0.01                       | 0.9       | 0.05                  | 0.7      | NA                   | NA       |
| HbA <sub>1c</sub>                | 0.42                 | 0.002    | 0.37                       | 0.006     | 0.36                  | 0.008    | NA                   | NA       |
| eGFR                             | 0.43                 | <0.001   | -0.4                       | 0.001     | -0.3                  | 0.02     | NA                   | NA       |
| CMR parameters                   |                      |          |                            |           |                       |          |                      |          |
| LVEF                             | -0.27                | 0.03     | -0.31                      | 0.02      | -0.09                 | 0.5      | 0.02                 | 0.9      |
| LVEDVI                           | 0.22                 | 0.08     | 0.32                       | 0.01      | -0.02                 | 0.9      | 0.22                 | 0.4      |
| LVESVI                           | 0.28                 | 0.03     | 0.37                       | 0.002     | 0.03                  | 0.8      | 0.18                 | 0.4      |
| LVEDMI                           | 0.09                 | 0.4      | 0.17                       | 0.2       | -0.05                 | 0.7      | 0.32                 | 0.2      |
| LVCi                             | 0.25                 | 0.04     | 0.23                       | 0.02      | 0.20                  | 0.1      | 0.06                 | 0.8      |
| RVEF                             | -0.17                | 0.2      | -0.14                      | 0.3       | -0.16                 | 0.2      | 0.23                 | 0.3      |
| RVEDVI                           | 0.12                 | 0.4      | 0.16                       | 0.2       | -0.006                | 1.0      | -0.13                | 0.6      |
| RVESVI                           | 0.16                 | 0.2      | 0.17                       | 0.2       | 0.1                   | 0.5      | -0.29                | 0.2      |
| RVEDMI                           | 0.34                 | 0.005    | 0.39                       | 0.002     | 0.15                  | 0.3      | 0.23                 | 0.4      |
| RVCi                             | 0.15                 | 0.2      | 0.15                       | 0.2       | 0.09                  | 0.5      | -0.08                | 0.7      |
| RAESVI                           | 0.28                 | 0.03     | 0.7                        | 0.03      | 0.18                  | 0.2      | -0.2                 | 0.8      |
| RAEDVI                           | 0.28                 | 0.03     | 0.28                       | 0.04      | 0.16                  | 0.2      | -0.06                | 0.8      |
| LAESVI                           | 0.28                 | 0.03     | 0.28                       | 0.09      | 0.26                  | 0.04     | 0.06                 | 0.4      |
| LAEDVI                           | 0.27                 | 0.03     | 0.26                       | 0.04      | 0.17                  | 0.2      | 0.07                 | 0.8      |
| LV global longitudinal strain    | -0.34                | 0.006    | -0.35                      | 0.005     | -0.19                 | 0.1      | -0.16                | 0.5      |
| LV global circumferential strain | -0.32                | 0.009    | -0.33                      | 0.008     | -0.19                 | 0.1      | -0.08                | 0.7      |
| RV global longitudinal strain    | -0.23                | 0.07     | -0.14                      | 0.3       | -0.27                 | 0.03     | -0.28                | 0.2      |

BMI, body mass index; BP, blood pressure; BSA, body surface area; CK-MB, creatine kinase muscle–brain fraction; CMR, cardiac magnetic resonance; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, glycated haemoglobin; HF, heart failure; LAEDVI, left atrial end-diastolic volume index; LAESVI, left atrial end-systolic volume index; LV, left ventricular; LVCi, left ventricular cardiac index; LVEDMI, left ventricular end-diastolic mass index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; NA, not available; NT-proBNP, N-terminal pro-brain natriuretic peptide; RAEDVI, right atrial end-diastolic volume index; RAESVI, right atrial end-systolic volume index; RV, right ventricular; RVCi, right ventricular cardiac index; RVEDMI, right ventricular end-diastolic mass index; RVEDVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume index.

\*P-value comparing total epicardial fat volume with patient characteristics and CMR parameters in HF.

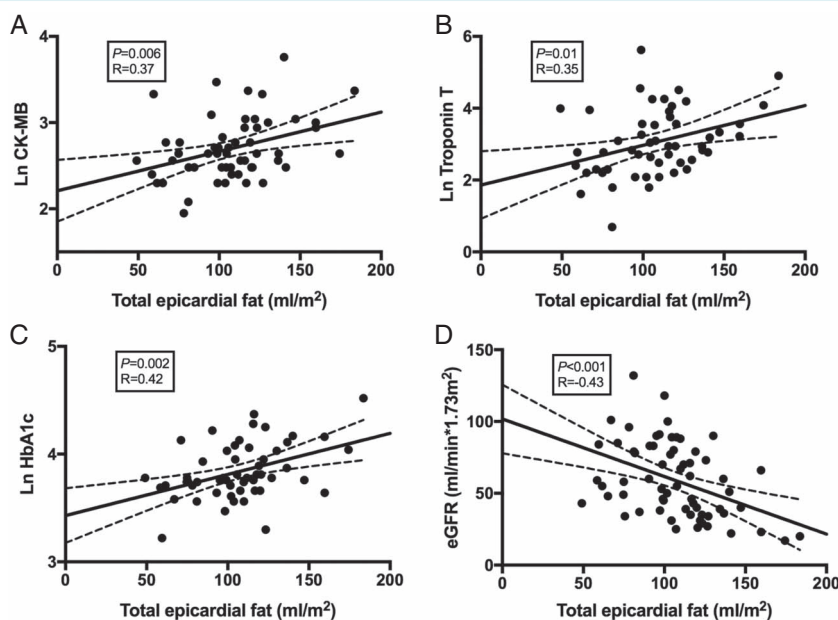
\*\*P-value comparing ventricular epicardial fat volume with patient characteristics and CMR parameters in HF.

†P-value comparing atrial epicardial fat volume with patient characteristics and CMR parameters in HF.

‡P-value comparing total epicardial fat volume with patient characteristics and CMR parameters in controls.

not available to measure pericardial restraint and ventricular interdependence. Furthermore, a recent study demonstrated a close relation between adipose tissue and left atrial electromechanical disturbances in HF.<sup>29</sup> To the best of our knowledge, this is the

first study demonstrating an association between epicardial fat and the presence of atrial fibrillation in patients with HFpEF. Atrial fibrillation may often predispose symptomatic HFpEF.<sup>30</sup> However, any causal relation between epicardial fat, the development



**Figure 3** Regression plots between total epicardial adipose tissue volumes and Ln CK-MB (A), Ln troponin T (B), Ln HbA<sub>1c</sub> (C), and eGFR (D). CK-MB, creatine kinase muscle–brain fraction; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, glycated haemoglobin.

of atrial fibrillation and onset or progression of HFpEF needs further study.

Type 2 diabetes mellitus has previously been associated with visceral fat around the organs and our finding that epicardial fat is increased in patients with type 2 diabetes mellitus supports this relation.<sup>31</sup> Additionally, the increased HbA<sub>1c</sub> and decreased eGFR levels associated with increased epicardial fat in our cohort are in line with this relation. Co-morbidities such as atrial fibrillation and type 2 diabetes mellitus are common in HF and are thought to influence HF through microvascular inflammation.<sup>4,6,32</sup> We observed an association between epicardial fat, HF with LVEF >40%, atrial fibrillation and type 2 diabetes mellitus. It is however unclear whether epicardial fat is a cause or a consequence of these diseases, or even merely an innocent bystander. Further studies are needed to unravel these relationships.

In our cohort, epicardial fat was negatively associated with left ventricular strain measurements. Whether epicardial fat has a direct effect on left ventricular systolic contractility is still unclear and needs to be studied more thoroughly.

Our findings support the idea that epicardial fat may induce inflammation, which is related to HF and the HF-predominant co-morbidities such as atrial fibrillation and type 2 diabetes mellitus. Epicardial fat may therefore be a marker for the inflammatory state in HF, atrial fibrillation and type 2 diabetes mellitus.

## Limitations

The present study has several limitations. First, the presence of pericardial effusion could not be ruled out entirely when quantifying epicardial fat on CMR. However, epicardial fat measurements

were in correspondence with the T1 times for fat, and not water. In addition, recent echocardiography was checked for pericardial effusion, which was not observed in these HF patients, therefore minimising the chance of overestimation of epicardial fat. Second, the sample size is relatively small, therefore the chance of false-positive outcomes increases. Also, due to the relatively small sample size we were not able to investigate extensive multivariable associations with epicardial fat. Third, due to the cross-sectional, retrospective nature of the study, we could not explore direct causal relations between epicardial fat, co-morbidities, biomarkers, and myocardial function and contractility. Fourth, our hypothesis that epicardial fat-associated inflammation leads to myocardial stiffness and HF with LVEF >40% is not supported by a relationship between epicardial fat and CRP or leucocytes, measured via peripheral venepuncture. The effects of epicardial fat may be too small to be picked up via a peripheral venepuncture, or total sample size is too small to pick up these signals. Lastly, data on the control group are limited, so only our primary question could be answered, and not any additional questions.

## Conclusions

Patients with HF with LVEF >40% have increased epicardial fat volume compared to controls. Epicardial fat is associated with type 2 diabetes mellitus and atrial fibrillation. In addition, epicardial fat is associated with biomarkers of myocardial damage, glucose levels, and renal dysfunction. Further research should focus on the potential cause–effect relationship between epicardial fat, co-morbidities, and myocardial damage in HF.



## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Patient characteristics based on HFmrEF and HFpEF.

**Table S2.** Cardiac magnetic resonance characteristics based on HFmrEF and HFpEF.

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